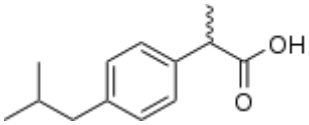
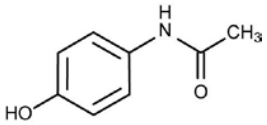
PRODUCT INFORMATION

i) Name of the medicine

NUROMOL®
ibuprofen 200mg and paracetamol 500mg film coated tablets

Chemical structure:





Ibuprofen
CAS: 15687-27-1
Molecular formula: $C_{13}H_{18}O_2$
MW: 206.3

Paracetamol
CAS: 103-90-2
Molecular formula: C8H9NO2
MW:151.16

ii) Description

Ibuprofen: Chemical name: 2-(4-Isobutylphenyl) propionic acid. It is a white or almost white powder or crystals with a characteristic odour. Practically insoluble in water, soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether and 1 in 1.5 of acetone; soluble in aqueous solutions of alkali hydroxides and carbonates.

Paracetamol: Chemical name: N-(4-hydroxyphenyl)acetamide. White or almost white crystalline powder. Odourless. Sparingly soluble in water (14 g/l (20 ºC)), freely soluble in alcohol, very slightly soluble in methylene chloride.

Nuromol tablets: A white to off-white, pearlescent, oval shaped, film coated tablet de-bossed with an identifying helix.

Excipients in *Nuromol tablets* : microcrystalline cellulose, croscarmellose sodium, Opadry II complete film coating system 85F18422, Opadry fx special effects film coating system 63F97546 silver, magnesium stearate, stearic acid, colloidal anhydrous silica.

iii) Pharmacology

The pharmacological actions of ibuprofen and paracetamol differ in their site and mode of action. These complementary modes of action result in greater antinociception than the single actives alone.

Ibuprofen possesses analgesic, antipyretic and anti-inflammatory properties, similar to other non-steroidal anti-inflammatory drugs (NSAIDs). Its mechanism of action is unknown, but it is thought to be through peripheral inhibition of cyclooxygenases and subsequent prostaglandin synthetase inhibition.

Paracetamol is a para-aminophenol derivative that exhibits analgesic and antipyretic activity. Paracetamol has minimal anti-inflammatory action. The precise mechanism of action remains

uncertain; it is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system.

Pharmacokinetics

Absorption
Ibuprofen is well absorbed from the gastrointestinal tract and is extensively bound to plasma proteins. Ibuprofen diffuses into the synovial fluid. Plasma levels of ibuprofen from this product are detected from 5 minutes with peak plasma concentrations achieved within 1-2 hours after ingestion on an empty stomach. When taken with food, peak plasma levels are delayed by a median of 25 minutes, but the overall extent of absorption is equivalent.

Paracetamol is readily absorbed from the gastrointestinal tract. Plasma protein binding is negligible at usual therapeutic concentrations, although this is dose-dependent. Plasma levels of paracetamol from this product are detected from 5 minutes with peak plasma concentrations occurring at 0.5-0.67 hours after ingestion on an empty stomach.

Metabolism
Ibuprofen is metabolised in the liver to two major metabolites with primary excretion via the kidneys, either as such or as major conjugates, together with a negligible amount of unchanged ibuprofen.

Paracetamol is metabolised in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates, with about 10% as glutathione conjugates. A minor hydroxylated metabolite, which is usually produced in very small amounts by mixed function oxidases in the liver and detoxified by conjugation with liver glutathione, may accumulate following paracetamol overdose and cause liver damage.

Excretion
Excretion of ibuprofen by the kidney is both rapid and complete. The elimination half-life is approximately 2 hours.

Less than 5% of paracetamol is excreted as unchanged paracetamol. The elimination half-life is approximately 3 hours.

No significant differences in the paracetamol or ibuprofen pharmacokinetic profiles are observed in the elderly.

The bioavailability and pharmacokinetic profiles of ibuprofen and paracetamol taken individually are not altered when taken in combination as a single or repeat dose.

iv) Clinical trials

Preclinical safety data

The toxicological safety profiles of ibuprofen and paracetamol individually have been established in animal experiments and in humans from extensive clinical experience. No new preclinical data in relation to the combination of ibuprofen and paracetamol is available.

Summary of clinical data

Randomised, double-blind, placebo-controlled studies were conducted with the combination using the acute pain model of post-operative dental pain.

Study 1
This efficacy study was a two part study (a single dose phase and a multiple dose phase). Seven hundred and thirty five subjects with post-operative dental pain were randomised to one of eight treatment groups in Part 1 (placebo, ibuprofen 200 mg or 400 mg, paracetamol 500 mg or 1000 mg, ibuprofen 100 mg plus paracetamol 250 mg (½ tablet Nuromol), ibuprofen 200 mg plus paracetamol 500 mg (1 tablet Nuromol) or 400 mg ibuprofen plus 1000 mg paracetamol (2 tablets Nuromol)).

In Part 1 of the study (single-dose phase), the primary efficacy variable was the mean differences in the sum of total pain relief and pain intensity difference (SPRID 0-8h) for pairwise comparisons.

Primary efficacy variable comparisons during Part 1 (single dose) all favoured the combination product over the comparators – that is, 2 tablets of Nuromol were more effective than 400 mg ibuprofen, 1000 mg paracetamol or placebo, and 1 tablet of Nuromol was more effective than 200 mg ibuprofen, 500 mg paracetamol or placebo. The majority of the secondary efficacy endpoints (including pain relief intensity difference 8 hours post dose, subjects overall assessment of medication, time to meaningful pain relief, duration of effects, and total pain relief over 8 hours) were consistent with the primary efficacy findings.

Seven hundred and fifteen subjects entered Part 2 (multiple dose phase) of the pivotal study, which involved only combinations – ½, 1 or 2 tablets of Nuromol – (no single actives) against placebo. The primary efficacy endpoint was the number of completed 24-hour periods with no more than one dose of rescue medication and with the subject's overall assessment always rated as at least good, in subjects who had taken the combination treatment or placebo in both parts 1 and 2 of the study.

One or two tablets of Nuromol were statistically significantly superior to placebo for the primary efficacy endpoint. The secondary efficacy variables (including time to treatment failure, duration between doses, peak pain relief and median score for subjects overall assessment) showed mixed results, with 1 tablet of Nuromol not significantly different to placebo for all parameters.

In Part 1, subjects taking either the 1 or 2 tablet doses of Nuromol experienced significantly fewer adverse effects than the placebo group, and subjects taking the 1 tablet dose of Nuromol also experienced significantly fewer adverse events than the 500 mg paracetamol group, with no significant differences in adverse events between any other groups. For the study overall, there were no significant differences in adverse events between any treatment groups. The most common adverse events in all groups were swelling face, nausea, vomiting and headache.

Study 2
An exploratory, single dose, efficacy and safety study in 234 subjects with post-operative dental pain was also conducted**.** The double blind, double-dummy study compared 400 mg ibuprofen plus 1000 mg paracetamol (equivalent to 2 tablets Nuromol) with 200 mg ibuprofen plus 500 mg paracetamol (equivalent to 1 tablet Nuromol), 400 mg ibuprofen, 1000 mg paracetamol and placebo.

Both doses of the combination treatment were significantly more efficacious as assessed by the primary efficacy parameter, SPRID (0-8 hr) than placebo and 1000 mg paracetamol. The higher dose combination (equivalent to 2 tablets of Nuromol), but not the lower dose combination (equivalent to 1 tablet Nuromol), was significantly more efficacious than 400 mg ibuprofen.

Both combination treatments were significantly more efficacious than placebo for the majority of secondary efficacy variables (including total pain relief (TOTPAR), sum of pain intensity difference (SPID) and SPRID over 0-4, 0-6 and 0-8 hours, peak pain relief and time to pain relief). The secondary efficacy variables showed mixed results for the comparisons of the combination treatments with ibuprofen 400 mg and paracetamol 1000 mg.

Each of the treatments was well tolerated and the adverse event profiles of the combination treatments were comparable to that of either drug administered alone.

Study 3
A double-blind, single dose, placebo-controlled, randomised study compared 1 or 2 tablets of Nuromol with a combination of paracetamol 1000 mg plus codeine 30 mg (2 tablets Panadeine Extra®) and ibuprofen 400 mg plus codeine 25.6 mg (2 tablets Nurofen Plus®) in 678 subjects with post-operative dental pain.

The study was conducted in subjects >16 years of age with moderate to severe pain.

The primary efficacy endpoint was the sum of the mean scores of pain relief (PR) combined with pain intensity (PI) differences over 12 hours (SPRID 0–12 h), i.e. the sum of the PI difference and the PR score integrated over the follow-up time period).

This study showed that for the primary efficacy variable, after a single dose over a 12 hour evaluation period, 1 tablet of Nuromol was statistically significantly more efficacious than 2 tablets of Panadeine Extra® or placebo, and non-inferior in analgesic effect to 2 tablets of Nurofen Plus®. Similar results were observed for the majority of the secondary efficacy parameters (which included SPRID over 4, 6 and 8 hours, SPID over 4, 6, 8 and 12 hours, TOTPAR over 4, 6, 8 and 12 hours, peak pain relief and pain intensity difference, subjects overall assessment, and time of onset and duration of action), although there were no differences between any of the active treatment groups in time to meaningful pain relief.

Fewer treatment emergent, and treatment-related treatment emergent adverse events occurred with both 2 tablets of Nuromol (ibuprofen 400 mg plus paracetamol 1000 mg) and 1 tablet of Nuromol (ibuprofen 200 mg plus paracetamol 500 mg) compared with Nurofen Plus®, Panadeine Extra® and placebo. All these comparisons achieved statistical significance with the exception of 1 tablet of Nuromol when compared with placebo. The adverse event profile was consistent with patients having undergone third molar extraction and no safety issues were raised.

An additional study examined the efficacy and safety of the combination on an alternative pain model, primary dysmenorrhoea.

Study 4
A double blind, randomised, crossover, single dose, single centre study examined the analgesic efficacy and tolerability of Nuromol in 94 subjects with primary dysmenorrhoea. Subjects received one of the following treatments: Nuromol (1 tablet) + placebo (1 tablet); Nuromol (2 tablets); or placebo (2 tablets).

The study was conducted in females >18 years of age with primary dysmenorrhoea with moderate to severe cramping pain in at least 4 of the previous 6 months.

The primary efficacy endpoint was total pain relief over 0-6 hours (TOTPAR6). Secondary endpoints included TOTPAR over 2 and 4 hours, SPRID over 2, 4 and 6 hours, SPID over 2, 4 and 6 hours, and subject's overall assessment of medication. For the primary efficacy variable, 2 tablets of Nuromol was significantly superior to placebo. The superiority of 1 tablet of Nuromol over placebo was borderline, with statistical superiority achieved for the protocol but not the intention-to-treat populations. For the secondary efficacy variables, the 2 tablet dose of Nuromol was significantly superior to placebo for the majority of parameters over 4 and 6 hours but not 2 hours, and the 1 tablet dose was superior to placebo for the majority of parameters over 6 hours but not 2 or 4 hours. Both active treatments were significantly superior to placebo for subject's overall assessment of medication, with treatments rated as good, very good or excellent in 63.3%, 57.8% and 43.4% for the 2 tablets of Nuromol, 1 tablet of Nuromol and placebo groups, respectively.

There were no withdrawals due to adverse events. Both the higher and lower dose combinations were well tolerated. The incidence of events did not differ with either treatment compared to placebo. Eleven patients reported 14 events (13 mild, 1 moderate) after taking the lower dose combination, seven patients reported 7 events (all mild) after taking the higher dose combination and nine patients reported 13 events (7 mild, 6 moderate) after taking placebo. There were no clinically significant laboratory abnormalities and no changes in vital signs during the course of the study.

v) Indications

Nuromol is indicated for the temporary relief of acute (short term) pain and/or inflammation associated with headache, migraine headache, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, period pain, sore throat, tennis elbow, rheumatic pain and arthritis, and the aches and pains associated with colds and flu.

vi) Contraindications

This product is contraindicated:

- In patients with a known hypersensitivity to ibuprofen, paracetamol or any other constituent of the medicinal product
- In patients with a history of hypersensitivity reactions (e.g. bronchospasm, angioedema, rhinitis or urticaria) associated with aspirin or other anti-inflammatory drugs or analgesic drugs.
- In patients with a history of, or an existing gastrointestinal ulceration/perforation or bleed, or other stomach disorder.
- In patients with impaired hepatic function, impaired renal function or heart failure
- In patients with asthma
- In pregnancy
- In patients with conditions that predispose to renal failure
- In concomitant use with ibuprofen or other NSAID-containing products, including cyclooxygenase-2 (COX-2) specific inhibitors and aspirin or other anti-inflammatories as there is an increased risk of adverse reactions

In concomitant use with other paracetamol-containing products as there is an increased risk of serious adverse effects; patients should be advised not take with any other paracetamol containing products. Immediate medical advice should be sought if this occurs, even if they feel well, as this can result in an overdose.

- In patients aged 65 years and over and in children under 12 years
- In patients undergoing treatment of perioperative pain in setting of coronary artery bypass surgery (CABG)

vii) Precautions

The hazard of paracetamol overdose is greater in patients with non-cirrhotic alcoholic liver disease. Immediate medical advice should be sought in the event of an overdose, even if the patient feels well, because of the risk of delayed, serious liver damage. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

Diabetes
Caution is required in patients suffering from diabetes. Paracetamol falsely elevates continuous blood glucose monitor (CGM) readings compared to finger stick (BG meter) readings. This is applicable for those using CGM devices with or without an automated insulin delivery pump e.g. in type I diabetes.

Respiratory disorders
Caution is required in patients with a history of bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm. The product is contraindicated in asthma (see under Contraindications above).

Renal and hepatic impairment
The administration of NSAIDs may cause a dose-dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. The product is contraindicated in patients with impaired renal or liver function or heart failure and in patients 65 years of age or older (see under Contraindications above).Renal function should be monitored in other at risk patients.

As with other NSAIDs elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged or may resolve with continued therapy. Meaningful elevations (three times the upper limit of normal) of ALT or AST occurred in controlled clinical trials in less than 1% of patients.

Patients should be advised to remain alert for hepatotoxicity and be informed about the signs and/or symptoms of hepatotoxicity (e.g. nausea, fatigue, lethargy, pruritus, jaundice, abdominal tenderness in the right upper quadrant and “flu-like” symptoms).

Cardiovascular and cerebrovascular effects
Observational studies have indicated that NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use.

Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk.

Patients should be advised to remain alert for such cardiovascular events, even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Fluid retention, hypertension and oedema have been reported in association with NSAID therapy. Patients taking antihypertensives with NSAIDs may have an impaired antihypertensive response. Appropriate monitoring and advice are required for patients with a history of hypertension. The product is contraindicated in patients with heart failure (see Contraindications above).

Clinical trial data suggest that the use of ibuprofen, particularly at high doses (2400 mg daily) may be associated with an increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. <1200mg daily) is associated with an increased risk of myocardial infarction.

Patients with uncontrolled hypertension, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Nuromol after careful consideration. Similar consideration should be made before initiating treatment for patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking). The product is contraindicated in heart failure (see under Contraindications above).

Gastrointestinal bleeding, ulceration and perforation
Gastrointestinal (Gl) bleeding, ulceration and perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious Gl events.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs), or antiplatelet agents.

The product is contraindicated in patients with a history of GI toxicity including ulceration (see Contraindications above).

When Gl bleeding or ulceration occurs in patients receiving Nuromol, the treatment should be withdrawn.

SLE and mixed connective tissue disease
In patient with systemic lupus erythematosus (SLE) and mixed connective tissue disease disorders there may be an increased risk of aseptic meningitis.

Dermatological
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN), have been reported very rarely in association with the use of NSAIDs and paracetamol. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Use of this product should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility
The use of the product may impair female fertility and is not recommended in women attempting to conceive.

Use in Pregnancy: Category C
Drugs which owing to their pharmacological effects have caused or may be suspected of causing harmful effects on the human foetus or neonate without causing malformation. These effects may be reversible.

There is no experience of use of this product in humans during pregnancy. Therefore this product is contraindicated for use during pregnancy.

Congenital abnormalities have been reported in association with NSAID administration in man; however these are low in frequency and do not appear to follow any discernible pattern. Use of NSAIDs during the last trimester of pregnancy may cause effects on the foetal cardiovascular system (risk of closure of ductus arteriosus), and the onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child.

Epidemiological studies in human pregnancy have shown no ill effects due to paracetamol use at the recommended dosage.

Lactation
Ibuprofen and its metabolites can pass in very small amounts (0.0008% of the maternal dose) into the breast milk. No harmful effects to infants are known.

Paracetamol is excreted in breast milk but not in a clinically significant amount. Available published data do not contraindicate breastfeeding.

Therefore it is not necessary to interrupt breastfeeding for short term treatment with the recommended dose of this product.

Paediatric use
Nuromol is contraindicated in children under 12 years of age since no investigations have been carried out with this product in this age group.

Use in the elderly
Nuromol is contraindicated in adults aged 65 years and over.

Genotoxicity
No information is available regarding Nuromol and genotoxicity.

Carcinogenicity
No information is available regarding Nuromol and carcinogenicity.

Effects on laboratory tests
No information is available regarding Nuromol and laboratory tests.

viii) Interaction with other medicines

This product is contraindicated in combination with:

- Aspirin,
- Other paracetamol containing products
- Other NSAIDs including cyclo-oxygenase-2 selective inhibitors
- Other anti-inflammatories and analgesics

as concomitant use may increase the risk of adverse reactions.

This product (like any other paracetamol containing products) should be used with caution in combination with:

- Chloramphenicol: increased plasma concentration of chloramphenicol
- Cholestyramine: the speed of absorption of paracetamol is reduced by cholestyramine. Therefore, cholestyramine should not be taken within one hour if maximal analgesia is required
- Metoclopramide and domperidone: the absorption of paracetamol is increased by metoclopramide and domperidone. However, concurrent use need not be avoided
- Warfarin: the anticoagulant effect of warfarin and other coumarins may be enhanced by prolonged regular use of paracetamol with increased risk of bleeding; occasional doses have no significant effect

This product (like any other ibuprofen containing products and NSAIDs) should be used with caution in combination with:

- Anticoagulants: NSAIDs may enhance the effects of anticoagulants, i.e. warfarin
- Antihypertensives: NSAIDs may reduce the effects of these drugs
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding
- Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma glycoside levels
- Ciclosporin: increased risk of nephrotoxicity
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding
- Diuretics: reduced diuretic effect. Diuretics may increase the risk of nephrotoxicity of NSAIDs
- Lithium: decreased elimination of lithium
- Methotrexate: decreased elimination of methotrexate
- Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone
- Quinolone antibiotics: animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions
- Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus
- Zidovudine: increased risk of haematological toxicity when NSAIDS are given concomitantly with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV+ haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

ix) Adverse effects

Clinical trials with this product have not indicated any other undesirable effects other than those for ibuprofen or paracetamol alone.

In clinical trials, the product administered in single or multiple doses was shown to have a safety profile comparable to that of placebo. The percentage of subjects who experienced side effects, as well as the individual side effects seen, were similar to the well documented profiles of paracetamol and ibuprofen administered alone.

The following is a list of adverse effects from pharmacovigilance data experienced by patients taking ibuprofen alone or paracetamol alone in short term and long term use.

Adverse events may be minimized by using the minimum effective dose for the shortest duration necessary to control symptoms.

Common (occur in >1% and <10%)
Gastrointestinal: abdominal pain, diarrhoea, dyspepsia, nausea, stomach discomfort and vomiting.
Investigations: alanine aminotransferase increased, gammaglutamyltransferase increased and liver function tests abnormal with paracetamol. Blood creatinine increased and blood urea increased.

Uncommon (occur in >0.1% and <1%)
Gastrointestinal: flatulence and constipation, peptic ulcer, perforation or gastrointestinal haemorrhage, with symptoms of melaena, haematemesis sometimes fatal, particularly in the elderly. Ulcerative stomatitis and exacerbation of ulcerative colitis and Crohn's disease. Less frequently gastritis has been observed and pancreatitis reported.
Skin and subcutaneous tissue disorders: rashes of various types (including urticarial) and pruritis. Angioedema and swelling face. Acute generalised exanthematous pustulosis.
Investigations: aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine increased, haemoglobin decreased and platelet count increased.
Nervous system disorders: headache and dizziness.

Very rare (occur in <0.01%)
Blood and lymphatic system disorders: haematopoietic disorders (agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leucopaenia, neutropaenia, thrombocytopaenia and pancytopaenia). First signs are fever, sore throat, superficial mouth ulcers, flu-like symptoms, severe exhaustion, unexplained bleeding and bruising and nose bleeds.
Immune system disorders: hypersensitivity reactions have been reported. These may consist of non-specific allergic reactions and anaphylaxis. Symptoms of severe hypersensitivity reactions can include facial, tongue and larynx swelling, dyspnoea, tachycardia, hypotension, anaphylaxis, angioedema or severe shock.
Psychiatric disorders: confusion, depression and hallucinations.
Nervous system disorders: paraesthesia, optic neuritis and somnolence. Single cases of aseptic meningitis in patients with existing autoimmune disorders (e.g. systemic lupus erythematosus and mixed connective tissue disease) during treatment with ibuprofen, with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation have been observed.
Eye disorders: visual disturbance.
Ear and labyrinth disorders: tinnitus and vertigo.
Cardiac disorders: oedema, hypertension and cardiac failure have been reported in association with NSAID treatment. Clinical trial and epidemiological data suggest that use of ibuprofen, particularly at high doses (2400 mg daily), and in long term treatment may be associated with a small increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke).
Respiratory, thoracic and mediastinal disorders: respiratory reactivity including asthma, exacerbation of asthma, bronchospasm and dyspnoea.
Hepatobiliary disorders: abnormal liver function, hepatitis and jaundice. In overdose, paracetamol can cause acute hepatic failure, hepatic failure, hepatic necrosis and liver injury.

Skin and subcutaneous tissue disorders: hyperhidrosis, purpura and photosensitivity. Exfoliative dermatoses. Bullous reactions including bullous erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Renal and urinary disorders: nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, and acute and chronic renal failure.
General disorders and administration site conditions: fatigue and malaise.

Hypersensitivity reactions have been reported following treatment with both paracetamol and ibuprofen. These may consist of:
a) Non-specific allergic reactions and anaphylaxis.
b) Respiratory tract reactivity e.g. asthma, aggravated asthma, bronchospasm and dyspnoea.
c) Assorted skin disorders, including rashes of various types, pruritius, urticaria, purpura, angioedema and more rarely bullous dermatoses (including toxic epidermal necrolysis and bullous erythema multiforme).

x) Dosage and administration

Adults under 65 and children from 12 years: 1 tablet every 8 hours as necessary (maximum 3 tablets in 24 hours). Keep to the recommended dose. Nuromol should not be used for more than 3 days at a time (or not more than 2 days at a time for adolescents aged 12 to 17 years) unless on medical advice, in which case the patient should be reviewed regularly with regard to efficacy, risk factors and ongoing need for treatment.

- Not recommended for children under 12 years of age.
- Not recommended for adults 65 years and over.

Monitoring advice: if symptoms persist please consult your healthcare professional.

xi) Overdosage

In case of overdose, immediately contact the Poisons Information Centre in Australia on 13 11 26 for advice.

Paracetamol
Liver damage is possible in adults who have taken 10 g (equivalent to 20 tablets) or more of paracetamol. Ingestion of 5 g (equivalent to 10 tablets) or more of paracetamol may lead to liver damage if the patient has one or more of the risk factors below:
a) Is on long term treatment with carbamazepine, phenobarbitone, phenytoin, primidone, rifampicin, St John's Wort or other drugs that induce liver enzymes.
b) Regularly consumes alcohol in excess of recommended amounts.
c) Is likely to be glutathione depleted e.g. eating disorders, cystic fibrosis, HIV infection, starvation, cachexia.

Symptoms
Symptoms of paracetamol overdose in the first 24 hours include pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion as liver function tests become abnormal. Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema and death. Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported.

Management
Immediate treatment is essential in the management of paracetamol overdose. Despite a lack of significant early symptoms, patients should be referred to hospital urgently for immediate medical attention. Symptoms may be limited to nausea or vomiting and may not reflect the severity of overdose or the risk of organ damage. Management should be in accordance with established treatment guidelines.

Treatment with activated charcoal should be considered if the overdose has been taken within 1 hour. Plasma paracetamol concentration should be measured at 4 hours or later after ingestion (earlier concentrations are unreliable).

Treatment with N-acetylcysteine may be used up to 24 hours after ingestion of paracetamol, however the maximum protective effect is obtained up to 8 hours post-ingestion. The effectiveness of the antidote declines sharply after this time.

If required, the patient should be given intravenous N-acetylcysteine in line with the established dosage schedule. If vomiting is not a problem, oral methionine may be a suitable alternative for remote areas, outside hospital.

Patients who present with serious hepatic dysfunction beyond 24 hours from ingestion should be managed in accordance with established guidelines.

Ibuprofen
Symptoms
Most patients who have ingested clinically important amounts of NSAIDs will develop no more than nausea, vomiting, epigastric pain, or more rarely diarrhoea. Tinnitus, headache and gastrointestinal bleeding are also possible. In more serious poisoning, toxicity is seen in the central nervous system, manifesting as drowsiness, occasionally excitation and disorientation or coma. Occasionally patients develop convulsions. In serious poisoning, metabolic acidosis may occur and prolong the prothrombin time (PT) and increase the international normalised ratio (INR), probably due to interference with the actions of circulating clotting factors. Acute renal failure and liver damage may occur if there is co-incident dehydration. Exacerbation of asthma is possible in asthmatics.

Management
Management should be symptomatic and supportive and include the maintenance of a clear airway and monitoring of cardiac and vital signs until stable. Consider oral administration of activated charcoal if the patient presents within 1 hour of ingestion of a potentially toxic amount. If frequent or prolonged, convulsions should be treated with intravenous diazepam or lorazepam. Give bronchodilators for asthma.

xii) Presentation and storage conditions

Dosage form: Nuromol is available in off-white, pearlescent, oval-shaped film coated tablets de-bossed with an identifying helix.

Quantity, proportion or strength of each therapeutically active ingredient: Nuromol tablets contain 200mg of ibuprofen and 500mg of paracetamol.

Container type: Nuromol tablets are packed in an aluminium blister pack.

Pack sizes:

Commercial pack sizes of Nuromol tablets: 6, 12 & 24
Registered pack sizes of Nuromol tablets: 2, 4, 5, 6, 8,10,12,16, 20 and 24

Storage conditions:
Store below 30ºC

xiii) Name and address of the sponsor

RECKITT BENCKISER AUSTRALIA PTY LTD
Level 47, 680 George Street, SYDNEY, 2000

xiv) Poison schedule of the medicine

Pharmacist-only medicine (S3) pack sizes of: 16, 20, 24, 30
Pharmacy Medicine (S2) pack sizes of: 2,3,4,5,6,8,9,10,12

xv) Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

4 July 2014

xvi) Date of most recent amendment
24 October 2017